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GUEST EDITORIAL

On to the Next Phase of Molecular Diagnostics—The Ultimate Laboratory Test

In Observance of the 20th Anniversary of the Annual Meeting of the Association for Molecular Pathology

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A highly condensed history of molecular biology could be said to have begun with the foundational work that led to Watson's and Crick's seminal discovery of the double helical nature of DNA. A golden age of molecular biology followed during which time tools were developed that became integral to the laboratory medicine discipline that has come to be known, more or less synonymously, as molecular diagnostics, molecular genetics, and molecular pathology. (In a nod toward this taxonomic elasticity, the American Board of Pathology and the American Board of Medical Genetics recognized, in 2001, subspecialty credentialing using the cumbersome but ecumenical term *molecular genetic pathology*.) Restriction endonuclease digestion, nucleic acid hybridization, Southern and Northern blotting, positional cloning, PCR and other *in vitro* nucleic acid amplification technologies, DNA sequencing, and other tools were seized upon by laboratorians to ignite this revolutionary field. The innovative approaches these molecular tools enabled have been applied, to lesser or greater degrees, in nearly all branches of medicine, serving as but a prelude to the inevitability of genomic applications even more broadly in the future. Has molecular diagnostics been transformative? The answer is arguable, but the path toward a positive answer seems clear. Does a quick *Star Trek*–like medical tricorder scan of the patient in the emergency department to learn his or her pharmacogenomic profile before drugs are administered sound as crazy in 2014 as it did in 1994? Think about what the answer to that question might be in 2034.

In keeping with the great tradition of science that all discoveries rest on the shoulders of giants, Y.W. Kan and his team, in the late 1970s, applied some of these technologies in the diagnosis of thalassemias[1] and hemoglobinopathies[2] or, put another way, molecular diagnostics was born. Soon thereafter, Southern blotting became an important adjunctive diagnostic tool for genotyping leukemias and lymphomas. The assessment of HER-2/*neu* gene amplification in node-positive breast cancer, as described by Slamon et al[3] using Southern blots in 1989, not only paved the way for breast cancer prognostication but also planted the seeds for precision medicine and other terms that became commonplace 20 years later (ie, companion diagnostics and targeted therapy). During this same two-decade period, the application of PCR to the detection of infectious agents transformed the test menus of all microbiology and virology laboratories and created some of the most high-volume, high-impact molecular pathology tests (eg, quantitative HIV and hepatitis C virus monitoring and detection of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and human papillomavirus).

It was apparent in the late 1980s to several visionaries in academic pathology that the tools of molecular biology would notably change the practice of laboratory medicine. Their efforts at organizing the community through various molecular diagnostics and molecular pathology meetings of practitioners are well documented by the first executive

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officer of the Association for Molecular Pathology (AMP), Dr. Frances Pitlick, in the October 2004 issue of the *AMP Newsletter* (*http://www.amp.org/about/newsletters/archive/10thann-04.pdf*, last accessed June 23, 2014). The birth of AMP in 1995 gave a societal home to the professionals practicing the tools of genomics, even before we knew to call it that.

Prospectively, 20 years is a long time. Retrospectively, it is the blink of an eye. Sixty years ago, the discovery of the double helical nature of DNA had only been in the scientific literature for a year. Forty years ago, although we knew how to purify DNA, the first tools of molecular biology (eg, restriction endonucleases) were being used, but the mainstays of molecular pathology investigation (eg, Southern blotting, nucleic acid amplification, and sequencing) had not yet been developed. Twenty years ago, the evolution from conventional to real-time PCR was in its infancy,[4] and the herculean effort of sequencing the human genome was less than half done.

Today, molecular pathologists are once again at the forefront of the evolution of laboratory medicine investigation as we move from amplification-based assays for detection of single analytes and static array–based assays for low-, medium-, and high-density panels to the ultimate laboratory test: the newest iteration of DNA sequencing. Alternatively called next-generation sequencing and massively parallel shotgun sequencing, it seems clear that the adjective *next generation* will have to change. Sequencing today is the harbinger of the ultimate laboratory test. Many or most, perhaps even all, molecular pathology questions, whether diagnostic, prognostic, therapeutic, or for monitoring, have their answers locked in the genome or exome, and next-generation DNA sequencing is the key to those answers. The technology is already being applied clinically hundreds of thousands of times annually for noninvasive detection in pregnant women of fetal aneuploidy or euploidy and, at lesser frequency, in oncology and cardiology workups. DNA sequencing, the ultimate genomic laboratory tool, will be as ubiquitous in 20 years as the microscope has been for anatomical pathology, hematology-oncology, and microbiology; indeed, DNA sequencing is the genomic equivalent of the microscope.

That molecular pathologists are the stewards of this new technology augurs well for the AMP, its members, and the physicians and patients we serve. We, as members and readers of *The Journal of Molecular Diagnostics*, look forward to reading the 2034 version of this article celebrating AMP's 40th anniversary to learn if our predictions rang true.

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